**In the Claims:**

Please insert claims 44 and 66, without prejudice, as presented below in amended form:

44. (Amended) A composition comprising a nucleic acid and at least two fatty acids or pharmaceutically acceptable salts thereof, wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution; a 2'-methoxyethoxy modification; a phosphorothioate linkage and a cytosine to 5-methyl-cytosine substitution; or a phosphorothioate linkage and a 2'-methoxyethoxy modification.

66. (Amended) A method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and at least two fatty acids, or pharmaceutically acceptable salts thereof, wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution; a 2'-methoxyethoxy modification; a phosphorothioate linkage and a cytosine to 5-methyl-cytosine substitution; or a phosphorothioate linkage and a 2'-methoxyethoxy modification.

## REMARKS

Upon entry of the amendment, claims 25-27, 44-50, 53-55, 57-64, 66-77, and 79-82 will be pending. Claims 44 and 66 have been amended to more clearly define the invention. No new matter has been added.

As a preliminary matter, Applicants request that the finality of the Office Action be withdraw, as it is improper. Contrary to the assertion in the Office Action, the amendments set forth in the response filed on January 22, 2002 did ***not*** necessitate a new ground of rejection. Applicants direct the Examiner's attention to the Remarks section on page 3 of the January 22$^{nd}$ response, which notes that the amendments in the response filed August 14, 2001 ***were not entered***. The amendments in the January 22$^{nd}$ response are ***identical*** to those previously presented in the August 14$^{th}$ response (*i.e.*, cancellation of claims 40, 56 and 78, amendment of claims 25, 50, 54, 61, 63, 64, 66, 74, 76 and 80, addition of claim 82). Thus, the amendments that allegedly necessitated a new ground of rejection are amendments that should already have been entered. This is not a proper basis for a final rejection. Accordingly, Applicants request withdrawal of the finality of the present Office Action.

**I. Rejection under 35 U.S.C. 112, first paragraph**

Claims 25-27, 40, 66-77, and 79-82 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement.[1] Applicants traverse the rejection and request reconsideration thereof because one skilled in the art would not require undue experimentation to practice the claimed inventions. As set forth in MPEP Section 2164.04, the Examiner bears the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. . . . It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

*MPEP* §2164.04 (emphasis added). The Office Action asserts that antisense technology is complex and unpredictable and that the specification allegedly does not teach treatment or investigation of the role of a gene or gene product. Applicants respectfully disagree.

The Office Action acknowledges that the specification does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway. (*See* Office Action, page 4). This is further supported by the declaration of Dr. Hardee and Dr. Teng (the "Hardee declaration"), which demonstrates that the claimed pharmaceutical compositions enhance penetration of a nucleic acid across the alimentary canal. Specifically, paragraphs 3-5 of the Hardee declaration describe experiments whereby penetration of an oligonucleotide across the alimentary canal of rats and dogs is enhanced by delivery of the oligonucleotide along with at least two fatty acids. Such examples are also set forth in Applicants' specification in Examples 3, 4 and 13. Accordingly, the specification enables the claimed methods of enhancing penetration of an antisense nucleic acid across the alimentary canal.

Applicants also submit that, contrary to the assertions in the Office Action, antisense technology is not highly unpredictable. Applicants submit herewith the declaration of Dr. Mark K. Wedel to support Applicants' assertion that antisense technology is a predictable art and

[1] As a preliminary matter, claim 40 was rejected although it is no longer pending in the present application. Claim 40 was cancelled in the response filed January 22, 2002.

would not require undue experimentation on the part of one of ordinary skill in the art to practice the claimed inventions. Dr. Wedel's declaration reports a phase I/II dose ranging human clinical trial was conducted of an ICAM-1 antisense oligonucleotide, ISIS 2302, in an enema formulation for ulcerative colitis. The results of the trial indicated that the antisense enema formulation had significant therapeutic results, as measured by the decrease in the median disease activity index and the median clinical activity index. Thus, those of ordinary skill in the art having read the present specification would be able to make and/or use the claimed antisense nucleic acid formulations for alimentary delivery without undue experimentation and with a reasonable expectation of success in delivery and therapeutic effectiveness of the nucleic acid.

The clinical trials in the Wedel declaration demonstrating the therapeutic effectiveness of antisense formulations and the Hardee declaration demonstrating that the claimed pharmaceutical compositions enhance penetration of a nucleic acid across the alimentary canal provide ample evidence that the claimed inventions are enabled. In the absence of evidence proving non-enablement of the present claims, Applicants respectfully request withdrawal of the rejection.

The Office further alleges "delivery of an antisense nucleic acid to the alimentary canal of an animal lacks a utility *per se*." (*See* Office Action at page 7-8). According to the Office, "the delivery of an antisense nucleic acid across the intestinal mucosal also [allegedly] does not have a utility, since the purpose of delivering an antisense nucleic acid across the intestinal mucosal is one step in the delivery of the antisense nucleic acid for some real-world purpose... Therefore, ***lack of enablement does not concern delivery of an antisense across the intestinal mucosal.***" (Office Action, page 8) Applicants respectfully disagree that the delivery of an antisense nucleic acid across a membrane or to the alimentary canal of an animal lacks a utility *per se.* The present specification enables a person of ordinary skill in the art how to make and use the claimed methods for enhancing the penetration of an antisense nucleic acid across the alimentary canal (claims 25-27) and how to make and use methods of delivering an antisense nucleic acid to the intestinal mucosal (claims 66-77 and 79-82). With this knowledge the person of ordinary skill in the art can then use the invention, for example, to investigate a gene or treat a disease as was demonstrated by the clinical trials described in the Wedel declaration. Thus, the claims have a "real world" use. Indeed, "enhancing the penetration" or "delivering an antisense nucleic acid" as it is recited in the pending claims is useful in itself, and also can be employed in a variety of ancillary methods which are very useful -- *e.g.* to treat a disease, investigate a gene's

function, or even to use a nucleic acid as a probe in localization studies. Further, no amount of undue experimentation is required to practice Applicants' claimed inventions. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

## II. Rejections under 35 U.S.C. § 102

### A. The Kitao Reference

Claim 61 stands rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by JP 57,080,314 to Kitao *et al.* (the "Kitao reference"). The Office Action asserts that the Kitao reference discusses a composition comprising a nucleic acid and capric or lauric acid in a pharmaceutically acceptable form, wherein the nucleic acid has a modified nucleobase or modified sugar residue. However, it will be recognized that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Calif*, 814 F.2d 628, 631 (Fed. Cir. 1987); *MPEP* § 2131. In addition, "the identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); *MPEP* § 2131. The Kitao reference does not disclose a nucleic acid, wherein the nucleic acid has a modified sugar residue. Rather, the Kitao reference discusses "amino sugar antibiotics," "polysaccharide antitumor substances," "peptide antibiotics," and "nucleic acid compounds," none of which are or suggest the claimed modified antisense nucleic acid (*see* Kitao reference, page 4). "Nucleic acid compounds" as described in the Kitao reference include "citicoline" and "nucleic acid antitumor substances," such as 5-Fu (*i.e.*, 5-fluorouracil). Citicoline is also known as CDP-choline or cytidine-5'-diphosphate choline and is an agent used to improve loss of consciousness due to head trauma and brain surgery. (*see* www.kyowa.co.jp/rd/stkrn.htm; a copy of which is submitted herewith). Furthermore, both citicoline and 5-Fu are ***monomers***. Accordingly, the Kitao reference does not anticipate the present claims, as it does not disclose or suggest nucleic acids (which are known in the artto be polynucleotides), let alone nucleic acids with a modified nucleobase or modified sugar residue. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be withdrawn.

**B. The WO 97/05903 reference (the Watts reference)**

Claim 61 stands rejected under 35 U.S.C. § 102(a) for allegedly anticipation by WO 97/05903 (the "Watts reference"). The Office action alleges that the Watts reference discusses a composition comprising a nucleic acid and capric acid in a pharmaceutically acceptable form, wherein the nucleic acid has a modified nucleobase or modified sugar residue. Applicants respectfully request that the rejection be withdrawn, as the Watts reference does not discuss a nucleic acid that has a modified nucleobase or modified sugar residue as recited in the claim. Rather, the Watts reference discusses "genes such as DNA or DNA constructs and antisense agents." (page 8, lines 11-12). The Watts reference does not disclose or suggest DNA having a modified nucleobase or modified sugar residue. As will be appreciated, absent a recitation of every element of the claim, a reference does not anticipate. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987); *MPEP* § 2131. Therefore, the Watts reference does not anticipate the claim. Applicants, therefore, respectfully request that thisrejection under 35 U.S.C. § 102(a) be withdrawn.

**C. U.S. Patent No. 5,707,648 (the Yiv Patent)**

Claims 25-27, 44-47, 49, 50, 53-55, 57-59, 61-64, 66-71, 73-77, and 79-82 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,707,648 to Yiv(the "Yiv patent"). The Office action alleges that the Yiv patent discloses "what is claimed in the present application." Applicants respectfully disagree, as the Yiv patent does not disclose the claimed invention.

The Yiv patent does not disclose a nucleic acid having a cytosine to 5-methyl cytosine substitution, or a 2'-methoxyethoxy modification (Claims 25, 44, 66 or 82) or a nucleic acid having a modified sugar residue (Claim 61). The remaining claims in the present application all depend either directly or indirectly on these claims, and, therefore, incorporate these elements. Because the Yiv patent does not disclose every element recited in the claims, it cannot anticipate the same. Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

**III. Rejection under 35 U.S.C. § 103(a)**

Claims 25-27, 44-50, 53-55, 57-64, 66-77, and 79-82 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Yiv patent in view of U.S. Patent No. 5,843,738 to Bennett et al. (the "Bennett reference"). However, as discussed above, the Yiv patent does not disclose the claimed cytosine to 5-methyl cytosine substitution, 2'-methoxyethoxy modification or a nucleic acid having a modified sugar residue. These deficiencies are not remedied by the teachings of the Bennett patent.

As is clear from MPEP §2143, in order to provide a *prima facie* case of obviousness, the Examiner must satisfy three criteria:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) ***must teach or suggest all the claim limitations.***

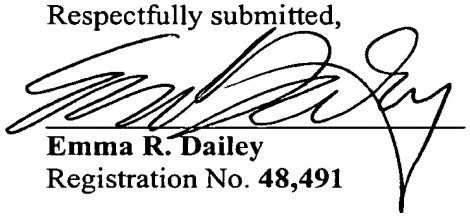
(MPEP §2143, emphasis added). With respect, Applicants assert that the Office Action has failed to satisfy these criteria.

As stated above, the Yiv patent does not disclose the composition recited in the claims– there simply is no disclosure or suggestion of the claimed modifications. Furthermore, there is no suggestion in either the Yiv or Bennett patents to modify the composition discussed in the Yiv patent to produce any claimed composition. The Bennett reference fails to suggest or motivate a person of ordinary skill in the art to modify the sugar residue (claim 61) or to modify the nucleic acid as recited in claims 44, 66, and 82. Therefore, even if a person of ordinary skill in the art would be motivated to combine the references, which he is not, the combination would not produce a claimed invention. In addition, the Office Action has pointed to no such motivation. The Yiv patent taken alone or in combination with the Bennett reference ***does not*** teach each and every element recited in the claims. Therefore, these references fail to make the present invention *prima facie* obvious. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

## IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of allowability is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative should there be any questions regarding Applicants' claimed invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



**Emma R. Dailey**
Registration No. **48,491**

Date: **October 9, 2002**

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the Claims:**

Please amend claims 44 and 66, without prejudice, as follows:

44. (Amended) A composition comprising a nucleic acid and at least two fatty acids or pharmaceutically acceptable salts thereof, wherein said nucleic acid has [at least one chemical modification selected from the group consisting of] a cytosine to 5-methyl-cytosine substitution ; [, a phosphorothioate linkage and] a 2'-methoxyethoxy modification; a phosphorothioate linkage and a cytosine to 5-methyl-cytosine substitution; or a phosphorothioate linkage and a 2'-methoxyethoxy modification.

66. (Amended) A method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and at least two fatty acids, or pharmaceutically acceptable salts thereof, wherein said nucleic acid has [at least one chemical modification selected from the group consisting of] a cytosine to 5-methyl-cytosine substitution ; [, a phosphorothioate linkage and] a 2'-methoxyethoxy modification; a phosphorothioate linkage and a cytosine to 5-methyl-cytosine substitution; or a phosphorothioate linkage and a 2'-methoxyethoxy modification.